Obstetric and perinatal outcome of babies born from vitrified oocytes

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Objective: To assess outcomes after oocyte vitrification on obstetric and perinatal outcomes compared with those achieved with fresh oocytes.
Design: Retrospective cohort study.
Setting: Private university-affiliated IVF center.
Patient(s): Children born after use of vitrified oocytes (1,027 from 804 pregnancies) and fresh oocytes (1,224 from 996 pregnancies). Singleton and multiples pregnancies from own and donated ova were included.
Intervention(s): Oocyte vitrification by the Cryotop method.
Main Outcome Measure(s): Pregnancy, delivery, and neonatal outcomes.
Result(s): Vitrification had no clinically relevant adverse effects on obstetric and perinatal outcomes after adjusting for potential confounders. No differences were found between the vitrified and fresh oocyte groups in the rate of obstetric problems (including diabetes, pregnancy-induced hypertension, preterm birth, anemia, and cholestasis), gestational age at delivery, birth weight, Apgar scores, birth defects, admission to neonatal intensive care unit (ICU), perinatal mortality, and puerperal problems. Only a greater number of invasive procedures (adjusted odds ratio 2.12; 95% confidence interval 1.41–3.20), and a reduced occurrence of urinary tract infection (adjusted odds ratio 0.51; 95% confidence interval 0.28–0.91), were observed in the vitrified oocytes group.
Conclusion(s): Although our data, the largest series to date, suggest that oocyte vitrification does not increase adverse obstetric and perinatal outcomes in children conceived with vitrified oocytes, further studies with larger samples are required to reinforce our conclusions. (Fertil Steril® 2014;102:1006–15. ©2014 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, oocyte vitrification, perinatal outcome, pregnancy problems

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A huge stride has been taken since the first report of pregnancy and live birth achieved after human oocyte cryopreservation and the present-day (1) when, thanks to the introduction of vitrification, this strategy has become a routine procedure in many IVF programs. Consequently, successful vitrification of the female gamete has been a milestone in assisted reproduction technology (ART), which has brought new horizons to treat infertile women, or even the fertile population who is at risk of losing their reproductive capacity owing to iatrogenic causes or age fertility decline. The availability of egg banking, capable of providing similar outcomes if compared with fresh oocyte cycles in ovum donation (2, 3), has conferred remarkable advantages to these programs. Similarly, autologous IVF cycles conducted with own vitrified oocytes has proven highly efficient (4–7). At present, reports on successful oocyte vitrification applications are increasingly frequent. Encouraged by these achievements, a growing number of women affected by cancer or other medical conditions has been offered the chance to vitrify oocytes to preserve their fertility (8). Another population, made up of women threatened by decline in fertility due to age who have decided to postpone motherhood for socioeconomic reasons, has also sought to take advantage of fertility preservation by means of oocyte vitrification. A recent study reports data on the clinical outcome of oocyte vitrification as a measure of fertility preservation for oncological and nononcological reasons, including data on live births (9). The widespread use of oocyte vitrification for all of these indications is responsible for the increasing number of live births

Received December 4, 2013; revised June 6, 2014; accepted June 12, 2014; published online July 23, 2014.
A.C. has nothing to disclose. V.S. has nothing to disclose. N.G. has nothing to disclose. I.O. has nothing to disclose. A.P. has nothing to disclose. J.R. has nothing to disclose.
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Fertility and Sterility® Vol. 102, No. 4, October 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.06.019

conceived with vitrified oocytes in a growing number of clinical settings.

Although vitrification has been revealed to be a highly effective tool in ART, continued monitoring of birth outcomes is strongly recommended to assess whether there is any risk associated with oocyte vitrification (8, 10). There are three main factors behind this admonition. First, some concerns about the vitrification procedure itself have been voiced. The main worries relate to the use of high concentrations of cryoprotectants required to achieve efficient vitrification (11). Toxic effects inherent to the use of high amounts of these substances have been overcome thanks to the development of new vitrification methods, which use very small volumes of vitrification solution and extreme cooling rates (12–14). This allows a significant reduction in the concentration of the cryoprotectants required to completely avoid ice crystallization (12). Some new generation devices, including the so-called open systems, require direct contact between samples and liquid nitrogen during vitrification. This factor has drawn attention to possible consequences of sample exposure to any element present in liquid nitrogen, regardless of it being of biological origin (i.e., contaminant-microorganisms or non biologigal residues). This is another major reason for the reluctance shown to this method, which has constrained its use in some countries. Second, the special architecture of mature oocytes renders them more sensitive to cryopreservation processes, and the analysis of perinatal outcome, as well as the long-term development of the children born, are necessary to rule out any adverse effect on offspring. Finally, the recent introduction of vitrification into the clinical practice makes it a novel strategy in ART and, as such, evaluation of the progeny is recommended to completely validate this approach. At present, these control procedures have been neglected in several newly introduced technologies used in ART (15, 16).

The current study aims to evaluate the safety of oocyte vitrification by analyzing obstetric and perinatal outcomes of the babies conceived after the transfer of vitrified oocytes and to compare these outcomes with those observed in pregnancies and live births achieved in IVF cycles conducted with fresh oocytes.

MATERIALS AND METHODS

Study Design and Study Population

This is a retrospective cohort study of the obstetric and perinatal data on the infants born after transferring embryos from either fresh (the control group) or vitrified (the study group) oocytes. The study was approved by the Institutional Review Board at our institution.

The study comprises all the births for which we had notification during the period between January 2007 and May 2012. Despite the efforts made in sending various reminder messages, such notification was received from the referral doctors in 50.8% and 81.6% of the pregnant women treated in our center with cycles using fresh or vitrified oocytes, respectively. Accordingly, 2,281 infants (N = 1,823 deliveries) were included. Among them, 1,233 babies were conceived using fresh oocytes, whereas 1,048 were developed from vitrified oocytes. However, we were unable to retrieve information on the perinatal outcome of 23 pregnancies (30 infants lost in the follow-up: 9 children from the control group and 21 from the study group). Therefore, the final sample analyzed consisted of 1,224 newborn infants (N = 996 deliveries) in the control group and 1,027 (N = 804 deliveries) in the study group (Fig. 1). Our inclusion criteria were: live births or stillbirth at or beyond 24 weeks of gestation, singleton or multiple pregnancies, and conceptions using either own oocytes or ovum donation. The only exclusion criterion was occurrence of pregnancy loss before 24 weeks of gestation.

In all cases, the IVF cycle and the embryo transfer (ET) were performed at the University Institute IVI Valencia, Spain. However, women's pregnancies were controlled and they delivered in their original places of residence: Spain (55.2% of women from the fresh oocyte cohort, and 39.2% of the vitrified oocyte cohort), other European countries (43.8% and 58.7% of each cohort, respectively), or elsewhere (1.0% and 2.1%, respectively). Half of the Spanish women (52.7% and 50.4% in each cohort, respectively) were monitored and they delivered in Valencia, Spain. Women were managed during pregnancy and delivery according to local protocols.

IVF Procedures

The IVF cycles were performed according to standard procedures. Protocols for ovarian stimulation are described elsewhere for either autologous IVF cycles (5, 17, 18) or donors (3). In ovum donation cycles, endometrial preparation for recipients was conducted as previously described (3, 19). Oocytes from patients and donors were vitrified in the Cryotop device (Kitazato BioPharma) (12) as formerly described (3). In brief, oocytes were equilibrated at room temperature in 7.5% (vol/vol) ethylene glycol + 7.5% dimethylsulfoxide (DMSO). After re-expansion (~12 minutes), oocytes were transferred to the vitrification solution consisting of 15% ethylene glycol + 15% DMSO + 0.5 M sucrose. After 1 minute in this solution, oocytes were placed on the Cryotop strip in a minimum volume and were directly submerged in liquid nitrogen. For warming, the Cryotop was removed from liquid nitrogen and placed in 1.0 M sucrose in tissue culture media M 199 + 20% synthetic serum substitute (SSS) at 37°C. After 1 minute, oocytes were transferred to a solution containing 0.5 M sucrose at room temperature for 3 minutes. After two washes of 5 and 1 minute each, oocytes were maintained under standard culture conditions for 2 hours before insemination. All the cycles performed with the vitrified oocytes were inseminated by intracytoplasmic sperm injection (ICSI), whereas 94.7% (N = 943) of fresh oocytes were performed according to ICSI procedures and 5.3% (N = 53) were inseminated by conventional IVF in the control group. All the ETs were performed under ultrasound guidance. Both day 3 embryos and blastocyst transfers were performed.

Data Source and Outcome Measurements

Information on the past medical and obstetric history of women, as well as data on the IVF cycle, was obtained from the computerized clinical charts of the University IVI Institute Valencia, Spain. Data on pregnancies and deliveries were